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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/517,450

09/01/2005

Marc Donath

4614-0160PUS1

5584

2292 7590 04/18/2007  
BIRCH STEWART KOLASCH & BIRCH  
PO BOX 747  
FALLS CHURCH, VA 22040-0747

EXAMINER

DANG, IAN D

ART UNIT

PAPER NUMBER

1647

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
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3 MONTHS

04/18/2007

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/18/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

**Office Action Summary**

Application No.

10/517,450

Applicant(s)

DONATH, MARC

Examiner

Ian Dang

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>08/22/2005 and 12/09/2004</u> . | 6) <input checked="" type="checkbox"/> Other: <u>PTO-90C and revised notice</u> .       |

## DETAILED ACTION

### ***Status of Applicant, Amendments, and/or Claims***

The amendment of 09 December 2004 has been entered in full claims. Claims 4-5 are amended.

### ***Election/Restrictions***

Applicant's election with traverse of Group I, claims 1-5 and 8-12 in the communication filed on 03/07/2007 is acknowledged.

The traversal is on the ground that Giannoukakis et al. (1999) fails to teach the limitations of claim 1. Contrary to the examiner's position, Applicants allege that Groups I-II share the special technical feature directed toward the prophylaxis or treatment of type 2 diabetes based on the use of IL-1Ra, which is not taught or suggested by Giannoukakis et al. (1999) or the prior art.

Applicant's arguments are persuasive. The restriction requirement between Groups I and II is hereby *withdrawn*. Groups I (claims 1-5 and 8-12) and Group II (claims 6-7 and 13-14) share a special technical feature and are thus rejoined. Applicant timely traversed the restriction (election) requirement in the reply filed on March 7, 2007.

Claims 1-14 are pending and under examination.

### ***Sequence Compliance***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

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However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

See sequence compliance letter attached to the instant Office Action.

***Claim Rejections - 35 USC § 112 (Written Description)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 and 8-12 are drawn to an interleukin 1 receptor antagonist. Thus, the claims are genus claims. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Specifically, the specification does not clearly define an interleukin 1 receptor antagonist and all methods of using such. Thus, the scope of the claims includes numerous structural and functional variants, and the genus' are highly variant because a significant number of structural and functional differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish interleukin 1 receptor antagonists are missing from the disclosure. No common attributes identify the members of the

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genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, an interleukin 1 receptor antagonist is insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus for an interleukin 1 receptor antagonist and all methods of using such.

There is no description of the special features, which are critical to the structure and function of the genus claimed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify an interleukin 1 receptor antagonist encompassed by the limitations. Thus, no identifying characteristics or properties of the instant interleukin 1 receptor antagonist are provided such that one of skill would be able to predictably identify the encompassed variant biological and chemical entities recited in the methods of the instant claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

***Claim Rejections - 35 USC § 112 (Enablement)***

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) restoring glucose-stimulated insulin secretion in  $\beta$  islet cells exposed to high glucose in vitro by culturing the cells with IL-1Ra and PDTC (figure 6, page 6), measuring the expression of IL-1Ra in human islets and observing its down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and inhibiting  $\beta$  islet cell apoptosis and restoring  $\beta$  islet cell function in vitro comprising culturing the cells with IL-1Ra (figure 9, page 7; page 35-36), does not reasonably provide enablement for (1) the use of an Interleukin 1 receptor antagonist (IL-1Ra) or the use of pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal (2) a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breadth of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

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Nature of the invention and breath of the claims

The invention is drawn to (1) the use of an Interleukin 1 receptor antagonist (IL-1Ra) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal (2) a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra). The invention is broad because the recitation of claims 1-5 and 8-12 encompasses numerous isoforms of interleukin 1 receptor antagonist. Arend et al. (2000, cited in the IDS the last page mailed 08/22/2006) teach that the interleukin 1 receptor antagonist (IL1Ra) family includes one secreted isoform and three intracellular isoforms (page 160, Abstract).

Unpredictability and state of the art

The state of the art for the treatment of patients with Type 2 diabetes with insulin is well established, but the treatment and prevention of Type 2 diabetes with Interleukin 1 receptor antagonist (IL-1Ra) of pyrrolidinedithiocarbamate (PDTC) is not well characterized.

The specification discloses that glucose-induced  $\beta$ -cell production of IL-1b contributes to the glucotoxicity in human pancreatic islets by inducing apoptosis (Figures 1-4). The IL-1 receptor antagonist protected cultured human islets from the toxic effects of glucose (Figures 6, 7, and 9). These findings suggest that an inflammatory process in the process in the pathogenesis of glucotoxicity in type 2 diabetes and identify the IL-1b/NF-KB pathway as a target to preserve  $\beta$  cell mass and function in this condition.

Despite the results disclosed in the specification regarding IL-1b and IL1-Ra, Applicant acknowledges some unpredictability regarding the mechanism for IL-1b as a cause for diabetes. For instance, Applicant recites that further studies regarding the role of IL-1ra in type 2 diabetes are also contemplated to investigate the molecular link between the role of IL-1Ra and Type 2

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diabetes (page 28). In addition, these findings are controversial because other investigators have not been able to corroborate these results. For instance, Welsh et al. (2005) teach that it is unlikely that locally produced IL-1b is an important mediator of glucotoxicity to human islets and argues against the IL-1b-NF-KB-Fas pathway as a common mediator for b-cell death in type 1 and type 2 diabetes.

In addition, Donath et al. (2004, cited in the IDS on page 1 mailed 12/09/2004) recite that the accepted view is that the insulin insufficiency in Type 2 diabetes is caused by insulin deficiency and disturbed kinetics of secretion combined with impaired glucose stimulus-secretion coupling (page 581, right column, 2<sup>nd</sup> paragraph). In contrast to this view, Donath et al. (2004) hypothesize that diabetes is a spectrum of clinical conditions all of which arise from relative or absolute insulin deficiency that is caused by decreased functional beta cell mass (page 587, left column, last paragraph).

In addition, Donath et al. (2004, cited in the IDS on page 1 mailed 12/09/2004) teach that unraveling the pathways leading to beta-cell death and impaired function may provide the basis for innovative therapy of Type 2 diabetes (page 585, left column, beginning of third paragraph). Finally, Donath et al. (2003, cited in the IDS on the last page mailed 08/22/2005) teach that based on current thinking, modulation of the intra-islet inflammatory mediators in type 1 and 2 diabetes appears as promising approach. The progressive decline in functional  $\beta$ -cell mass observed in diabetic patients may thus be prevented and even reversed. However, it will take several years until drugs are available with the primary aim of preventing, the inflammatory process of islets (page 466, left column, middle of 2<sup>nd</sup> paragraph).

In view of these teachings in the art and the limited guidance provided in the specification, IL-1Ra and PDTC restoring glucose-stimulated insulin secretion in human islets exposed to high glucose (figure 6, page 6), the expression of IL-1Ra in human islets and its

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down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and IL-1Ra protecting  $\beta$ -cell apoptosis and restoring  $\beta$  cell function (figure 9, page 7), is not predictable for (1) the use of an interleukin 1 receptor antagonist (IL-1Ra) or the use of pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal (2) a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC).

The amount of direction or guidance present

Applicants' disclosure is limited to the *in vitro* studies investigating IL-1Ra and PDTC restoring glucose-stimulated insulin secretion in human islets exposed to high glucose (figure 6, page 6), measuring the expression of IL-1Ra in human islets and its down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and inhibiting  $\beta$  islet cell apoptosis and restoring  $\beta$  islet cell function with IL-1Ra (figure 9, page 7; page 35-36). However, the specification does not provide guidance or direction regarding (1) the use of an Interleukin 1 receptor antagonist (IL-1Ra) or the use of pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal (2) a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC).

Applicant has not provided any steps in preparing any medicament with the receptor antagonist (IL-1Ra) or PDTC, in testing the effectiveness of the medicament, or in administering and treating the medicament in an animal model for diabetes type 2 or in a human patient with type 2 diabetes.

Working Examples

Although Applicants have provided (1) restoring glucose-stimulated insulin secretion in  $\beta$  islet cells exposed to high glucose in vitro by culturing the cells with IL-1Ra and PDTC (figure 6, page 6), measuring the expression of IL-1Ra in human islets and its down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and inhibiting  $\beta$  islet cell apoptosis and restoring  $\beta$  islet cell function in vitro with IL-1Ra (figure 9, page 7; page 35-36), the specification does not provide any methods or working examples for the use of an Interleukin 1 receptor antagonist (IL-1Ra) or the use of pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal or a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC).

On page 22 of the specification, Applicant suggests a protocol for the treatment of patients with type 2 Diabetes mellitus with interleukin-1 receptor antagonist. However, no studies were performed to test IL-1Ra as a therapeutic for type 2 diabetes. Moreover, the specification does not provide any methods or working examples for the treatment of patients of with type 2 diabetes with pyrrolidinedithiocarbamate (PDTC).

The quantity of experimentation needed

Without sufficient disclosure in the specification and the broad scope of the claims, it would require undue experimentation for one of skill in the art to be able to treat or prophylactically suppress type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or

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pyrrolidinedithiocarbamate (PDTC). In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to (1) the use of an Interleukin 1 receptor antagonist (IL-1Ra) or the use of pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal (2) a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need thereof a sufficient amount of an interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC).

***Claim Rejections - 35 USC § 112 (Second paragraph) and 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 1-7 provide for the use of an interleukin 1 receptor antagonist and of pyrrolidinedithiocarbamate (PDTC), but, since the claim does not set forth any steps involved in

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the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 11-12, and 13 recite the limitation "medicament" in line 1. There is insufficient antecedent basis for this limitation in the claims.

### **Prior Art**

The prior art is made of record and not relied upon is considered pertinent to Applicants' disclosure.

Maedler et al. (2002, cited in the IDS on page 1 mailed 12/09/2004) teach that the IL-1 receptor antagonist and PDTC protect cultured human islets from undergoing apoptosis induced by glucose (Figure 4, page 856).

### **Conclusion**

No claim is allowed.

### **Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang  
Patent Examiner  
Art Unit 1647  
March 28, 2007

*Bridget E. Bunner*

**BRIDGET BUNNER  
PATENT EXAMINER**



## UNITED STATES DEPARTMENT OF COMMERCE

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APPLICATION NO./ CONTROL NO. <b>10/517,450</b>	FILING DATE <b>09/01/2005</b>	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION <b>DONATH, Marc</b>	ATTORNEY DOCKET NO. <b>4614-0160PUS1</b>
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EXAMINER

Ian Dang

ART UNIT

PAPER

1647

20070327

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

At page 32 of the specification, the 4 oligonucleotides used as primers have not been assigned any SEQ ID No. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

## Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

*Bridget E. Bunner***BRIDGET BUNNER  
PATENT EXAMINER**

<b>Notice to Comply</b>	Application No. 10/517,450	Applicant(s) DONATH, MARC	
	Examiner Ian Dang	Art Unit 1647	

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.
- ☒ 7. Other: The 4 oligonucleotides used as primers disclosed at page 32 of the specification have not been assigned any SEQ ID No.

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923

For CRF Submission Help, call (703) 308-4212 or 308-2923

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